Legends for supplementary figures:

Figure S1. Grp78 is overexpressed in human tumors. Samples from HNSCC tumor were stained with Grp78 as described in materials and methods, and samples from NHM were used as negative control.

Figure S2. Proangiogenic factor expression is negatively correlated with glucose gradient in tumor cells. UM-SCC-81B cells were treated with gradient glucose (2, 6, 10, 12 and 25 mM) for 18 hours. Total mRNA was extracted from each sample. Expression of the UPR marker Grp78 and angiogenic mediators (VEGF, FGF2 and IL6) were determined with q-PCR.

Figure S3. UPR activation promotes expression of proangiogenic mediators in UM-SCC-11B and UM-SCC-17B cells. The two cell lines were treated with GD (glucose, 2 mM) for 24 hours, UPR readouts (PERK, XBP-1s and Grp78) were assessed with western blot (A), and expression of angiogenic factors VEGF (B), IL6 (C) and FGF2 (D) was determined by ELISA. *: p < 0.05.

Figure S4. Perk-knockout mouse embryonic fibroblasts (MEF) show decreased VEGF expression level upon GD. Perk/- MEF and Perk+/+ MEF (gift from Randal J. Kaufman’s Laboratory) were treated with GD (glucose, 2 mM) for 4 and
24 hours. A, western blot was used to determine PERK, CHOP and Grp78 expression. mRNA was extracted from the treated cells and q-PCR was used to determine ATF4 (B) and VEGF (C) expression levels. *: p < 0.05.

Figure S5. UPR regulates blood vessel formation and tumor progression. A, tumor weight (at end-point) was used to evaluate tumor growth rate. B, Ki67 and Grp78 expression in xenograft tumors was examined by IHC staining, and Ki67 expression was quantified. C, Blood vessel density was detected by factor VIII staining and defined as the number of blood vessels per-field. *: p < 0.05.

Figure S6. IL8 responds in a distinct manner to UPR activation compared to other proangioenic factors. A, GD (2mM), TM (1 μg/mL) and TG (100 nM) were used to treat tumor cells (UM-SCC-81B, MCF7 and U87) and VEGF secretion was measured with ELISA. B, In UM-SCC-81B cells, GD (2mM) and TM (1 μg/mL) could not induce IL8 expression; however TG (100 nM) induced significant IL8 expression.